

Response

S/N 09/644,387

Page -2-

As 8. (Amended) A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98.0% and containing less than 0.03% estradiol and less than 0.02% estrone.

21. (Amended) A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

protecting the 3- and 17-hydroxyl groups of estradiol;

reacting the protected estradiol with bromine and acetic acid to produce a 2-brominated derivative of estradiol;

reacting the 2-brominated derivative of estradiol with sodium methoxide in the presence of a copper catalyst;

removing the protecting groups on the 3- and 17-hydroxyl groups to produce 2-methoxyestradiol; and

As purifying the 2-methoxyestradiol using liquid chromatography on an adsorption/partition medium with a solvent system comprising a polar and a nonpolar solvent.

22. (Amended) A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

ring-brominating estradiol by reacting estradiol with bromine in the presence of acetic acid to produce a ring-brominated intermediate;

reacting the ring-brominated intermediate with sodium methoxide in the presence of a copper catalyst to produce 2-methoxyestradiol; and

purifying the 2-methoxyestradiol using liquid chromatography on an adsorption/partition medium with a solvent system comprising a polar and a nonpolar solvent.

23. (Amended) A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol

Response

S/N 09/644,387

Page -3-

having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

protecting the 3- and 17-hydroxyl groups of estradiol;

reacting the protected estradiol with nitric acid and acetic acid to produce a 2-nitro derivative of estradiol;

reducing the 2-nitro derivative of estradiol to produce the corresponding 2-amino derivative of estradiol;

reacting the 2-amino derivative of estradiol under Sandmeyer conditions to produce a 3-,17-hydroxyl protected 2-methoxyestradiol; and

removing the protecting groups on the 3- and 17-hydroxyl groups to produce 2-methoxyestradiol.

24. (Amended) A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

protecting the 3-hydroxyl group of estrone;

reacting the protected estrone with nitric acid and acetic acid to produce a 2-nitro derivative of estrone;

reducing the 2-nitro derivative of estrone to produce the corresponding 2-amino derivative of estrone;

reacting the 2-amino derivative of estrone under Sandmeyer conditions to produce a 3-hydroxyl protected 2-methoxyestrone;

removing the protecting group on the 3-hydroxyl group to produce 2-methoxyestrone; and

reducing the 17-keto group of 2-methoxyestrone to produce 2-methoxyestradiol.

25. (Amended) A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

*Response**S/N 09/644,387**Page -4-**Am Cond*

brominating estradiol in the presence of acetic acid to produce a mixture of ring-brominated estradiols;

isolating 2-bromoestradiol from the mixture of estradiols; and

reacting the 2-bromoestradiol with sodium methoxide in the presence of a copper catalyst to produce 2-methoxyestradiol.

ATLLIB02 70365.1